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      (FILE 'HOME' ENTERED AT 13:21:26 ON 04 SEP 2003)

      FILE 'MEDLINE, EMBASE, SCISEARCH, BIOSIS, USPATFULL' ENTERED AT 13:21:44
      ON 04 SEP 2003
L1          3228 S (GLYCOPROTEIN? OR GPIIBIIIA) (6P) ADENOSINE?
L2          3057 S (GLYCOPROTEIN? OR GPIIBIIIA) (3P) ADENOSINE?
L3             5 S (INHIBIT? (3A) ACTIVAT? (3A) (GLYCOPROTEIN? OR GPIIBIIIA)) (P
L4             2 DUP REM L3 (3 DUPLICATES REMOVED)
L5        376801 S ADENOSINE NOT (ADENOSINE DIPHOSPHATE)
L6          1922 S L2 AND L5
L7             3 S (INHIBIT? (3A) ACTIVAT? (3A) (GLYCOPROTEIN? OR GPIIBIIIA)) AN
L8             1 DUP REM L7 (2 DUPLICATES REMOVED)
L9           155 S (INHIBIT? (3A) (GLYCOPROTEIN? OR GPIIBIIIA)) AND L6
L10            0 S (INHIBIT? (3A) (GPIIBIIIA)) AND L6
L11           22 S GPIIBIIIA AND L6
L12           18 DUP REM L11 (4 DUPLICATES REMOVED)

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L12 ANSWER 1 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2003:225214 USPATFULL

TITLE: Novel methods of imaging and treatment with targeted compositions

INVENTOR(S): Unger, Evan C., Tucson, AZ, UNITED STATES
Wu, Yunqiu, Tucson, AZ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003157025	A1	20030821
APPLICATION INFO.:	US 2003-341167	A1	20030113 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-243640, filed on 3 Feb 1999, GRANTED, Pat. No. US 6521211 Division of Ser. No. US 1998-218660, filed on 22 Dec 1998, PENDING Continuation-in-part of Ser. No. US 1996-660032, filed on 6 Jun 1996, ABANDONED Continuation-in-part of Ser. No. US 1996-640464, filed on 1 May 1996, ABANDONED Continuation-in-part of Ser. No. US 1995-497684, filed on 7 Jun 1995, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-73913P	19980206 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103

NUMBER OF CLAIMS: 72

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 12 Drawing Page(s)

LINE COUNT: 7075

AB Novel ultrasound methods comprising administering to a patient a targeted vesicle composition which comprises vesicles comprising a lipid, protein or polymer, encapsulating a gas, in combination with a targeting ligand, and scanning the patient using ultrasound. The scanning may comprise exposing the patient to a first type of ultrasound energy and then interrogating the patient using a second type of ultrasound energy. The targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. The methods may be used to detect a thrombus, enhancement of an old or echogenic thrombus, low concentrations of vesicles and vesicles targeted to tissues, cells or receptors.

AB . . . targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. The methods may be used to detect a thrombus, enhancement of an old or echogenic thrombus, low concentrations of. . .

SUMM . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor.

DETD . . . immunoglobulins and cytoplasmic receptors for steroid hormones. An exemplary receptor within the context of the present invention is the glycoprotein **GPIIbIIIa**, which is a platelet integrin.

DETD . . . comprise a targeting ligand. Generally speaking, materials which may be employed as targeting ligands include, for example, proteins, including antibodies, **glycoproteins** and lectins, peptides, polypeptides, saccharides, including mono- and polysaccharides, vitamins, steroids, steroid analogs, hormones, cofactors, bioactive agents, and genetic material,. . .

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors. It is contemplated that

preferred targeting ligands for use in targeting tissues and/or receptors, including the tissues and receptors. . . from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material, including, for example, antibodies, **glycoproteins** and lectins, with peptides being preferred. An example of a protein which may be preferred for use as a targeting. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . known in the art. Targeting ligands derived or modified from human leukocyte origin, such as CD11a/CD18, and leukocyte cell surface **glycoprotein** (LFA-1), may also be used as these are known to bind to the endothelial cell receptor ICAM-1. The cytokine inducible. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. Conveniently, by attaching anti-myosin (particularly cardiomyosin) antibody. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD [0218] Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD . . . wide variety of targeting ligands may be employed to direct the present lipid compositions, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. In preferred form, the targeting ligand exhibits a binding affinity (Kd) to the **GPIIbIIIa** receptor of no greater than about 10.sup.-1 molar. More preferably, the targeting ligand exhibits a binding affinity (Kd) to the **GPIIbIIIa** receptor of less than about 10.sup.-3 molar such as, for example, binding affinities ranging from about 10.sup.-9 molar to less. . . subcombinations of ranges of binding affinities therein. Even more preferably, the targeting ligand exhibits a binding affinity (Kd) to the **GPIIbIIIa** receptor of from about 10.sup.-7 molar to about 10.sup.-5 molar, with a binding affinity of about 10.sup.-6 molar being especially. . .

DETD [0220] Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing, as well as treating such. . .

DETD [0222] Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1--(X.sup.1).sub.n-Arg-Tyr-Asp-(Y).sub.o--(X.sup.2).sub.m--R.sup.2, wherein each. . .

DETD [0229] Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD [0230] Generally speaking, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . the covalent linkage may be established and which is generally not critical for binding to the desired receptor, for example, **GPIIbIIIa** receptor. Also in the case of cyclized targeting ligands, the cyclization preferably exposes the backbone conformation and sidechain topography of. . . the sequences RGD or AGD, such as KQAGDV, to enable binding of the ligand to the receptor, such as the **GPIIbIIIa** receptor.

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in Sato et al., U.S. Pat. No. 5,498,601 and the following published European Patent Applications: 0. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, Q targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells,. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, T targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells and the glycoprotein **GPIIbIIIa** receptor. In addition, T is preferably selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents,. . .

DETD . . . of the vesicle. This may promote binding of the targeting ligands to targeting sites, for example, receptors, such as the **GPIIbIIIa** receptor, and tissues, including myocardial, endothelial and epithelial cells, since the targeting ligand has a greater likelihood of exposure to. . .

DETD [0532] **GPIIbIIIa** binding peptide (Integrated Biomolecule Corporation, Tucson, Ariz.) was covalently bonded to DPPE-PEG 3400 utilizing the procedure described above in Example. . . headspace replaced with perfluorobutane gas (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor.

DETD . . . be seen from the above table, binding was observed only with the vesicle composition prepared in Example 7 which contains **GPIIbIIIa** targeting peptide.

DETD . . . example is directed to the preparation of vesicles based on human serum albumin that bear targeting ligands directed to the **GPIIbIIIa** receptor.

DETD . . . suspension will be added 1% glutaraldehyde and 1% by weight of the peptide Lys-Gln-Ala-Gly-Asp-Val resulting in crosslinked perfluoropropane vesicles bearing **GPIIbIIIa** binding peptide.

DETD . . . example is directed to the preparation of vesicles stabilized by polymerizable acryloyl/styryl lipid analogs binding targeting ligands directed to the **GPIIbIIIa** receptor.

DETD [0540] To a solution in normal saline of DPPE-PEG 5000 (1.8 mg/mL) and 10% by weight DPPE-PEG-5000 labelled with **GPIIbIIIa** binding peptide (Lys-Gln-Ala-Gly-Asp-Val), which will be prepared using the procedure described above in Example 5, will be added compound (3). .

. room temperature for about 1 minute. The vesicle composition will be irradiated (254 nm) to provide polymerized gas-filled vesicles bearing **GPIIbIIIa** binding peptide. The mean diameter of the vesicles will be about 3 .mu.m.

DETD [0541] This example is directed to the preparation of synthetic polybis(carboxylatophenoxy)phosphazene) (PCPP) gas-filled vesicles targeted to the **GPIIbIIIa** receptor.

DETD . . . be crosslinked by the divalent calcium ions to produce a relatively homogeneous population of spherical gel vesicles, targeted to the **GPIIbIIIa** and filled with perfluoropropane. The presence of entrapped perfluoropropane will be demonstrated by observation of the vesicles using an inverted. . .

DETD [0544] This example is directed to the preparation of a vesicles targeted to the **GPIIbIIIa** receptor formulated form a fluorinated lipid.

DETD . . . will be suspended in phosphate-buffered saline at a pH of 7. The peptide Arg-Gly-Asp-Ser (RGDS), which is targeted to the **GPIIbIIIa** receptor, will be added to the suspension. After stirring overnight, the reaction mixture will be concentrated with an Amicon filter. . . an ESPE Capmix (ESPE, Seefeld, Germany) at 4300 rpm for 1 minute to yield the fluorinated vesicle targeted to the **GPIIbIIIa** receptor.

DETD . . . pad. After the unbound clot was washed from the strip, 1 mL each of a targeted vesicle composition which targets **GPIIbIIIa** and the vesicle composition from Example 6 (non-targeted) was injected into the PBS stream at a flow rate of approximately. . . strip, while the non-targeted vesicles were washed away. Ultrasound imaging revealed increased echogenicity in the clot with vesicles targeted to **GPIIbIIIa**.

CLM What is claimed is:

. . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor.

L12 ANSWER 2 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2003:120810 USPATFULL

TITLE: Modulators of pharmacological agents

INVENTOR(S): Sullenger, Bruce A., Durham, NC, UNITED STATES
Rusconi, Christopher P., Durham, NC, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003083294	A1	20030501	
APPLICATION INFO.:	US 2002-155233	A1	20020528	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-293231P	20010525	(60)
	US 2001-331037P	20011107	(60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: NIXON & VANDERHYE P.C., 8th Floor, 1100 North Glebe Road, Arlington, VA, 22201

NUMBER OF CLAIMS: 51

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 28 Drawing Page(s)

LINE COUNT: 3501

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The biological activity of nucleic acid ligand is regulated (i.e. enhanced or inhibited) in vivo to produce a desired biological effect. This is accomplished through the administration of a modulator, or regulator, that changes the binding of the nucleic acid ligand for its target or that degrades or otherwise cleaves, metabolizes or breaks down

the nucleic acid ligand while the ligand is still exerting its effect. Modulators of the present invention can be administered in real time as needed based on various factors, including the progress of the patient, as well as the physician's discretion in how to achieve optimal therapy. Thus, this invention provides for the first time a regulatable therapeutic regime in the course of nucleic acid ligand therapy.

DETD . . . pyrimidine bases substituted at the 6-position with sulfur or 5 position with halo or C.sub.1-5 alkyl groups, a basic linkers, 3'-deoxy-**adenosine** as well as other available "chain terminator" or "non-extendible" analogs (at the 3'-end of the RNA), or labels such as. . .

DETD . . . biomolecule that is the focus of a therapeutic drug strategy or diagnostic assay, including, without limitation, enzymes, enzyme inhibitors, hormones, **glycoproteins**, lipids, phospholipids, nucleic acids, intracellular, extracellular, and cell surface proteins, peptides, carbohydrates, including glycosaminoglycans, lipids, including glycolipids and certain oligonucleotides,. . .

DETD . . . acid ligands in flow cytometry; U.S. Pat. No. 5,849,890, entitled High affinity oligonucleotide ligands to chorionic gonadotropin hormone and related **glycoprotein** hormones; U.S. Pat. No. 5,849,479, entitled High-affinity oligonucleotide ligands to vascular endothelial growth factor (VEGF); U.S. Pat. No. 5,846,713, entitled. . . nucleic acid ligands and inhibitors; U.S. Pat. No. 5,837,456, entitled High affinity oligonucleotide ligands to chorionic gonadotropin hormone and related **glycoprotein** hormones; U.S. Pat. No. 5,834,199, entitled Methods of identifying transition metal complexes that selectively cleave regulatory elements of mRNA and. . . acid ligands in flow cytometry; U.S. Pat. No. 5,849,890, entitled High affinity oligonucleotide ligands to chorionic gonadotropin hormone and related **glycoprotein** hormones; U.S. Pat. No. 5,849,479, entitled High-affinity oligonucleotide ligands to vascular endothelial growth factor (VEGF); U.S. Pat. No. 5,846,713, entitled. . . nucleic acid ligands and inhibitors; U.S. Pat. No. 5,837,456, entitled High affinity oligonucleotide ligands to chorionic gonadotropin hormone and related **glycoprotein** hormones; U.S. Pat. No. 5,834,199, entitled Methods of identifying transition metal complexes that selectively cleave regulatory elements of mRNA and. . . entitled DNA encoding and 18 KD CDK6 inhibiting protein; U.S. Pat. No. 5,631,146, entitled DNA aptamers and catalysts that bind **adenosine** or **adenosine**-5'-phosphates and methods for isolation thereof; U.S. Pat. No. 5,629,407, entitled DNA encoding an 18 KD CDK6 inhibiting protein and antibodies. . .

DETD . . . (TF)/factor VIIa (FVIIa), factor VIIIa (FVIIIa)/factor IXa (FIXa), factor Va (FVa/factor Xa (Fxa) enzyme complexes and platelet receptors such as **gpIIbIIIa**, gpIbIX, gpVI, factors involved in promoting platelet activation such as Gas6, factors involved in promoting or maintaining fibrin clot formation. . .

CLM What is claimed is:

. . . molecule is a tissue factor (TF)/factor VIIa (FVIIa), factor VIIIa (FVIIIa)/factor IXa (FIXa), factor Va (FVa)/factor Xa (Fxa) enzyme complex, **gpIIbIIIa**, gpIbIX, gpVI, Gas6, PAI-1 (plasminogen activator inhibitor 1), coagulation factor XIIIa (FXIIIa), ATIII (anti-thrombin III), thrombin or coagulation factor XIa. . .

L12 ANSWER 3 OF 18 USPATFULL on STN

ACCESSION NUMBER:	2003:78107 USPATFULL			
TITLE:	Charged lipids and uses for the same			
INVENTOR(S):	Unger, Evan C., Tucson, AZ, UNITED STATES			
PATENT ASSIGNEE(S):	ImaRx Therapeutics, Inc. (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003054027	A1	20030320	
APPLICATION INFO.:	US 2002-46801	A1	20020115	(10)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-540448, filed on 31 Mar 2000, GRANTED, Pat. No. US 6403056 Division of Ser. No. US 1997-925353, filed on 8 Sep 1997, GRANTED, Pat. No. US 6120751 Continuation-in-part of Ser. No. US 1997-823791, filed on 21 Mar 1997, GRANTED, Pat. No. US 6143276 Continuation-in-part of Ser. No. US 1997-851780, filed on 6 May 1997, GRANTED, Pat. No. US 6090800 Continuation-in-part of Ser. No. US 1997-877826, filed on 18 Jun 1997, PENDING Continuation-in-part of Ser. No. US 1997-887215, filed on 2 Jul 1997, GRANTED, Pat. No. US 6028066
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Woodcock Washburn LLP, 46th Floor, One Liberty Place, Philadelphia, PA, 19103
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 5893
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to charged lipids, compositions comprising charged lipids, and the use of these compositions in drug delivery, targeted drug delivery, therapeutic imaging and diagnostic imaging, as well as their use as contrast agents.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors. Preferred targeting ligands for use in targeting tissues and/or. . . tissues and receptors exemplified above, are selected from the group consisting of proteins, including antibodies, antibody fragments, hormones, hormone analogues, **glycoproteins** and lectins, peptides, polypeptides, amino acids, sugars, such as saccharides, including monosaccharides and polysaccharides, and carbohydrates, vitamins, steroids, steroid analogs,. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD [0208] Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeting ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD [0209] A wide variety of targeting ligands may be employed to direct the present compositions to the **GPIIbIIIa** receptor. Compositions

which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing and treating such clots. Included. . .

DETD [0210] Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and. . .

DETD [0217] Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD [0218] Generally, it is preferred to employ, as targeting ligands for the **GPIIbIIIa** receptor, a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD [0227] Various peptides which would be suitable for use as a targeting ligand in the present invention, especially for targeting **GPIIbIIIa**, are described, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0368 486 A2, 0382451 A2, and 0. . .

DETD [0378] DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 4 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2003:102125 USPATFULL

TITLE: Thermal preactivation of gaseous precursor filled compositions

INVENTOR(S): Unger, Evan C., Tucson, AZ, United States

PATENT ASSIGNEE(S): Bristol-Myers Squibb Medical Imaging, Inc., Princeton, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6548047	B1	20030415	
APPLICATION INFO.:	US 1997-929847		19970915	(8)

DOCUMENT TYPE: Utility

FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Dudash, Diana L.

ASSISTANT EXAMINER: Sharareh, Shahnam

LEGAL REPRESENTATIVE: Woodcock Washburn LLP

NUMBER OF CLAIMS: 30

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)

LINE COUNT: 7034

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes, among other things, the surprising discovery that gaseous precursor filled compositions are profoundly more effective as acoustically active contrast agents when they are thermally preactivated to temperatures at or above the boiling point of the instilled gaseous precursor prior to their in vivo administration to a patient. Further optimization of contrast enhancement is achieved by administering the gaseous precursor filled compositions to a patient as an infusion. Enhanced effectiveness is also achieved for ultrasound mediated targeting and drug delivery.

DETD . . . activator (t-PA), glutathione, insulin, dopamine, peptide ligands containing RGD, AGD, RGE, KGD, KGE or KQAGDV (Peptides with affinity for the **GPIIBIIIa** receptor), opiate peptides, enkephalins, endorphins and their analogs, human chorionic gonadotropin

(HCG), corticotropin release factor (CRF), cholecystokinins and their analogs,. . .

DETD . . . of Ras. DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors. Preferred targeting ligands for use in targeting tissues and/or. . . tissues and receptors exemplified above, are selected from the group consisting of proteins, including antibodies, antibody fragments, hormones, hormone analogues, **glycoproteins** and lectins, peptides, polypeptides, amino acids, sugars, such as saccharides, including monosaccharides and polysaccharides, and carbohydrates, vitamins, steroids, steroid analogs,. . .

DETD . . . non-peptide angiogelic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine;. hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . used to target active plaque with evolving clots. Preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa** The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the hmman alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD . . . wide variety of targeting ligands may be employed to direct the present stabilizing materials, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing, as well as treating such. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2- aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also. . .

DETD Generally, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0 368 486 A2, 0 382 451. .

DETD **GPIIbIIIa** peptide (Integrated Biomolecule Corporation, Tucson, Ariz.) was covalently bonded to DPPE-PEG 3400 to produce DPPE-PEG-Lys-Gln-Ala-Gly-Asp- Val (SEQ ID NO: 39),. . .

DETD . . . headspace replaced with perfluoromethylbutyl ether (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor (hereafter "thrombus-targeting contrast agent").

L12 ANSWER 5 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2003:47498 USPATFULL
TITLE: Methods of imaging and treatment with targeted compositions
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
Wu, Yunqiu, Tucson, AZ, United States
PATENT ASSIGNEE(S): Bristol-Myers Squibb Medical Imaging, Inc., Princeton, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6521211	B1	20030218
APPLICATION INFO.:	US 1999-243640		19990203 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-218660, filed on 22 Dec 1998 Continuation-in-part of Ser. No. US 1996-660032, filed on 6 Jun 1996, now abandoned Continuation-in-part of Ser. No. US 1996-640464, filed on 1 May 1996, now abandoned Continuation-in-part of Ser. No. US 1995-497684, filed on 7 Jun 1995, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-73913P	19980206 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Travers, Russell
ASSISTANT EXAMINER: Sharareh, Shahnam
LEGAL REPRESENTATIVE: Woodcock Washburn LLP
NUMBER OF CLAIMS: 58
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT: 7580
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel ultrasound methods comprising administering to a patient a targeted vesicle composition which comprises vesicles comprising a lipid, protein or polymer, encapsulating a gas, in combination with a targeting ligand, and scanning the patient using ultrasound. The scanning may comprise exposing the patient to a first type of ultrasound energy and then interrogating the patient using a second type of ultrasound energy. The targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. The methods may be used to detect a thrombus, enhancement of an old or echogenic thrombus, low concentrations of vesicles and

vesicles targeted to tissues, cells or receptors.

AB . . . targeting ligand preferably targets tissues, cells or receptors, including myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. The methods may be used to detect a thrombus, enhancement of an old or echogenic thrombus, low concentrations of. . .

SUMM . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor.

DETD . . . immunoglobulins and cytoplasmic receptors for steroid hormones. An exemplary receptor within the context of the present invention is the glycoprotein **GPIIbIIIa**, which is a platelet integrin.

DETD . . . comprise a targeting ligand. Generally speaking, materials which may be employed as targeting ligands include, for example, proteins, including antibodies, **glycoproteins** and lectins, peptides, polypeptides, saccharides, including mono- and polysaccharides, vitamins, steroids, steroid analogs, hormones, cofactors, bioactive agents, and genetic material,. . .

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors. It is contemplated that preferred targeting ligands for use in targeting tissues and/or receptors, including the tissues and receptors. . . from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material, including, for example, antibodies, **glycoproteins** and lectins, with peptides being preferred. An example of a protein which may be preferred for use as a targeting. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . known in the art. Targeting ligands derived or modified from human leukocyte origin, such as CD11a/CD18, and leukocyte cell surface **glycoprotein** (LFA-1), may also be used as these are known to bind to the endothelial cell receptor ICAM-1. The cytokine inducible. .

.

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. Conveniently, by attaching anti-myosin (particularly cardiomyosin) antibody. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted.

. .

DETD . . . wide variety of targeting ligands may be employed to direct the present lipid compositions, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. In preferred form, the targeting ligand exhibits a binding affinity (Kd) to the **GPIIbIIIa**

receptor of no greater than about 10.sup.-3 molar. More preferably, the targeting ligand exhibits a binding affinity (Kd) to the **GPIIbIIIa** receptor of less than about 10.sup.-3 molar such as, for example, binding affinities ranging from about 10.sup.-9 molar to less. . .

DETD Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing, as well as treating such. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg--Tyr--Asp; also abbreviated RGD) Y, linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1--(X.sup.1).sub.n--Arg--Tyr--Asp--(Y).sub.o--(X.sup.2).sub.m--R.sup.2, wherein each. . .

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac--(D)Phe--Pro--boroArg and the cyclic peptidomimetic cyclo(D--2--aminobutyrate--N--Methyl--L--Arginyl--Glycyl--L--Aspartyl--3--amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . . Plasminogen activator inhibitor type 1 (PAI-1) are other useful ligands. Other synthetic compounds which may be useful for targeting the **GPIIbIIIa** receptor include, for example, ticlopidine, clopidogrel, tirofibran, and abciximab and analogs and derivatives thereof.

DETD Generally speaking, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . the covalent linkage may be established and which is generally not critical for binding to the desired receptor, for example, **GPIIbIIIa** receptor. Also in the case of cyclized targeting ligands, the cyclization preferably exposes the backbone conformation and sidechain topography of. . . AGD, such as KQAGDV SEQ ID NO. 1, to enable binding of the ligand to the receptor, such as the **GPIIbIIIa** receptor.

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in Sato et al., U.S. Pat. No. 5,498,601 and the following published European Patent Applications: 0. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, Q targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells and the glycoprotein **GPIIbIIIa** receptor. In addition, in embodiments where Q is a targeting ligand, Q is preferably selected from the group consisting of. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, T targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells and the glycoprotein **GPIIbIIIa** receptor. In addition, T is preferably selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents,. . .

DETD . . . of the vesicle. This may promote binding of the targeting ligands to targeting sites, for example, receptors, such as the **GPIIbIIIa** receptor, and tissues, including myocardial, endothelial and epithelial cells, since the targeting ligand has a

greater likelihood of exposure to. . .

DETD **GPIIbIIIa** binding peptide (Integrated Biomolecule Corporation, Tucson, AZ) was covalently bonded to DPPE-PEG 3400 utilizing the procedure described above in Example. . . headspace replaced with perfluorobutane gas (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor.

DETD . . . be seen from the above table, binding was observed only with the vesicle composition prepared in Example 7 which contains **GPIIbIIIa** targeting peptide.

DETD . . . example is directed to the preparation of vesicles based on human serum albumin that bear targeting ligands directed to the **GPIIbIIIa** receptor.

DETD . . . 1% glutaraldehyde and 1% by weight of the peptide Lys-Gln-Ala-Gly-Asp-Val SEQ ID NO. 1 resulting in crosslinked perfluoropropane vesicles bearing **GPIIbIIIa** binding peptide.

DETD . . . example is directed to the preparation of vesicles stabilized by polymerizable acryloyl/styryl lipid analogs binding targeting ligands directed to the **GPIIbIIIa** receptor.

DETD To a solution in normal saline of DPPE-PEG 5000 (1.8 mg/mL) and 10% by weight DPPE-PEG-5000 labelled with **GPIIbIIIa** binding peptide (Lys-Gln-Ala-Gly-Asp-Val SEQ ID NO. 1), which will be prepared using the procedure described above in Example 5, will. . . room temperature for about 1 minute. The vesicle composition will be irradiated (254 nm) to provide polymerized gas-filled vesicles bearing **GPIIbIIIa** binding peptide. The mean diameter of the vesicles will be about 3 .mu.m.

DETD This example is directed to the preparation of synthetic polybis(carboxylatophenoxy)phosphazene) (PCPP) gas-filled vesicles targeted to the **GPIIbIIIa** receptor.

DETD . . . be crosslinked by the divalent calcium ions to produce a relatively homogeneous population of spherical gel vesicles, targeted to the **GPIIbIIIa** and filled with perfluoropropane. The presence of entrapped perfluoropropane will be demonstrated by observation of the vesicles using an inverted. . .

DETD This example is directed to the preparation of a vesicles targeted to the **GPIIbIIIa** receptor formulated form a fluorinated lipid.

DETD . . . phosphate-buffered saline at a pH of 7. The peptide Arg-Gly-Asp-Ser (RGDS) SEQ ID NO. 2, which is targeted to the **GPIIbIIIa** receptor, will be added to the suspension. After stirring overnight, the reaction mixture will be concentrated with an Amicon filter. . .

DETD . . . an ESPE Capmix (ESPE, Seefeld, Germany) at 4300 rpm for 1 minute to yield the fluorinated vesicle targeted to the **GPIIbIIIa** receptor.

DETD . . . pad. After the unbound clot was washed from the strip, 1 mL each of a targeted vesicle composition which targets **GPIIbIIIa** and the vesicle composition from Example 6 (non-targeted) was injected into the PBS stream at a flow rate of approximately. . . strip, while the non-targeted vesicles were washed away. Ultrasound imaging revealed increased echogenicity in the clot with vesicles targeted to **GPIIbIIIa**.

CLM What is claimed is:

. . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor.

=> d l12 ibib ab kwic 6-10

L12 ANSWER 6 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2002:287094 USPATFULL
TITLE: Novel acoustically active drug delivery systems

INVENTOR(S): Unger, Evan C., Tucson, AZ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002159952	A1	20021031
APPLICATION INFO.:	US 2002-84855	A1	20020227 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-75343, filed on 11 May 1998, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-46379P	19970513 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Woodcock Washburn LLP, One Liberty Place - 46th Floor, Philadelphia, PA, 19103
NUMBER OF CLAIMS: 46
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 5458

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to targeted therapeutic delivery systems comprising a gas or gaseous precursor filled microsphere wherein said gas or gaseous precursor filled microsphere comprises an oil, a surfactant, and a therapeutic compound. Methods of preparing the targeted therapeutic delivery systems are also embodied by the present invention which comprise processing a solution comprising an oil and a surfactant in the presence of a gaseous precursor, at a temperature below the gel to liquid crystalline phase transition temperature of the surfactant to form gas or gaseous precursor filled microsphere, and adding to said microspheres a therapeutic compound resulting in a targeted therapeutic delivery system, wherein said processing is selected from the group consisting of controlled agitation, controlled drying, and a combination thereof.

DETD . . . tetrahydrofolate; peptides, such as angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the **GPIIbIIIa** receptor (usually found on activated receptor platelets) such as RGD, AGD, RGE, KGD, KGE, and KQAGDV, opiate peptides (such as. . .

DETD [0151] DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 7 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2002:72457 USPATFULL
TITLE: SOLID POROUS MATRICES AND METHODS OF MAKING AND USING THE SAME
INVENTOR(S): UNGER, EVAN C., TUCSON, AZ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002039594	A1	20020404
APPLICATION INFO.:	US 1998-75477	A1	19980511 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-46379P	19970513 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN KURTZ, MACKIEWICZ AND NORRIS, ONE LIBERTY PLACE 46TH FLOOR, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 106
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5207
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a solid porous matrix comprising a solvent and a surfactant in combination with a bioactive agent. The solvent and the surfactant may, if desired, form vesicles, an agglomeration of which comprises the matrix. The composition optionally comprises a gas or a gaseous precursor. The emulsion may be dried, and subsequently reconstituted in an aqueous or organic solution.

The present invention is also directed to a method of preparing a solid porous matrix comprising combining a solvent, a surfactant, and a therapeutic to form an emulsion; and processing the emulsion by controlled drying, or controlled agitation and controlled drying to form a solid porous matrix. The resulting solid porous matrix may also comprise a gas or gaseous precursor and be added to a resuspending medium.

A method for the controlled delivery of a targeted therapeutic to a region of a patient is another embodiment of the present invention. The method comprises administering to the patient a composition having a solid porous matrix comprising a solvent, a surfactant, a therapeutic, and a gas or gaseous precursor, monitoring the composition using energy to determine the presence of the composition in the region; and releasing the therapeutic from the composition in the region using energy.

DETD . . . tetrahydrofolate; peptides, such as angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the **GPIIbIIIa** receptor (usually found on activated receptor platelets) such as RGD, AGD, RGE, KGD, KGE, and KQAGDV, opiate peptides (such as. . .

DETD [0135] DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

CLM What is claimed is:

. . . the group consisting of angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the **GPIIbIIIa** receptor, opiate peptides, human chorionic gonadotropin, corticotropin release factor, cholecystokinins, bradykinins, promoters of bradykinins, inhibitors of bradykinins, elastins, vasopressins, pepsins,. . .

43. A composition of claim 42 wherein said peptides with affinity for the **GPIIBIIIa** receptor are selected from the group consisting of RGD, AGD, RGE, KGD, KGE, and KQAGDV.

L12 ANSWER 8 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2002:167866 USPATFULL
TITLE: Acoustically active drug delivery systems
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
PATENT ASSIGNEE(S): Bristol-Myers Squibb Medical Imaging, Inc., Princeton, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6416740	B1	20020709	
APPLICATION INFO.:	US 1998-75343		19980511	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1997-46379P	19970513	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Dudash, Diana
ASSISTANT EXAMINER: Sharareh, Shahnam
LEGAL REPRESENTATIVE: Woodcock Washburn LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 5660
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to targeted therapeutic delivery systems comprising a gas or gaseous precursor filled microsphere wherein said gas or gaseous precursor filled microsphere comprises an oil, a surfactant, and a therapeutic compound. Methods of preparing the targeted therapeutic delivery systems are also embodied by the present invention which comprise processing a solution comprising an oil and a surfactant in the presence of a gaseous precursor, at a temperature below the gel to liquid crystalline phase transition temperature of the surfactant to form gas or gaseous precursor filled microsphere, and adding to said microspheres a therapeutic compound resulting in a targeted therapeutic delivery system, wherein said processing is selected from the group consisting of controlled agitation, controlled drying, and a combination thereof.

DETD . . . tetrahydrofolate; peptides, such as angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the **GPIIbIIIa** receptor (usually found on activated receptor platelets) such as RGD, AGD, RGE, KGD, KGE, and KQAGDV, opiate peptides (such as. . .

DETD DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 9 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2002:136533 USPATFULL
TITLE: Method for delivering bioactive agents using cochleates
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
PATENT ASSIGNEE(S): Imarx Therapeutics, Inc., Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6403056	B1	20020611
APPLICATION INFO.:	US 2000-540448		20000331 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-925353, filed on 8 Sep 1997, now patented, Pat. No. US 6120751
Continuation-in-part of Ser. No. US 1997-823791, filed on 21 Mar 1997, now patented, Pat. No. US 6143276
Continuation-in-part of Ser. No. US 1997-851780, filed on 6 May 1997, now patented, Pat. No. US 6090800
Continuation-in-part of Ser. No. US 1997-877826, filed on 18 Jun 1997 Continuation-in-part of Ser. No. US 1997-887215, filed on 2 Jul 1997, now patented, Pat. No. US 6028066
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Hartley, Michael G.
LEGAL REPRESENTATIVE: Woodcock Washburn LLP
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 6445
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to charged lipids, compositions comprising charged lipids, and the use of these compositions in drug delivery, targeted drug delivery, therapeutic imaging and diagnostic

imaging, as well as their use as contrast agents.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors. Preferred targeting ligands for use in targeting tissues and/or. . . tissues and receptors exemplified above, are selected from the group consisting of proteins, including antibodies, antibody fragments, hormones, hormone analogues, **glycoproteins** and lectins, peptides, polypeptides, amino acids, sugars, such as saccharides, including monosaccharides and polysaccharides, and carbohydrates, vitamins, steroids, steroid analogs,. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeting ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD A wide variety of targeting ligands may be employed to direct the present compositions to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing and treating such clots. Included. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1--(X.sup.1).sub.n-Arg-Tyr-Asp-(Y).sub.o--(X.sup.2).sub.m--R.sup.2, wherein each. . .

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD Generally, it is preferred to employ, as targeting ligands for the **GPIIbIIIa** receptor, a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD Various peptides which would be suitable for use as a targeting ligand in the present invention, especially for targeting **GPIIbIIIa**, are described, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0 368 486 A2, 0 382 451. . .

DETD DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 10 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2001:182086 USPATFULL

TITLE: Novel methods of ultrasound treatment using gas or gaseous precursor-filled compositions

INVENTOR(S): Unger, Evan C., Tucson, AZ, United States

PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001031243	A1	20011018	
APPLICATION INFO.:	US 2001-813484	A1	20010321	(9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1997-929847, filed on 15 Sep 1997, PENDING			

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Woodcock Washburn Kurtz, Mackiewicz & Norris LLP, 46th Floor, One Liberty Place, Philadelphia, PA, 19103

NUMBER OF CLAIMS: 34

EXEMPLARY CLAIM: 1

LINE COUNT: 6360

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes, among other things, the surprising discovery that gaseous precursor filled compositions are profoundly more effective as acoustically active contrast agents when they are thermally preactivated to temperatures at or above the boiling point of the instilled gaseous precursor prior to their in vivo administration to a patient. Further optimization of contrast enhancement is achieved by administering the gaseous precursor filled compositions to a patient as an infusion. Enhanced effectiveness is also achieved for ultrasound mediated targeting and drug delivery.

DETD . . . of Ras. DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors. Preferred targeting ligands for use in targeting tissues and/or. . . tissues and receptors exemplified above, are selected from the group consisting of proteins, including antibodies, antibody fragments, hormones, hormone analogues, **glycoproteins** and lectins, peptides, polypeptides, amino acids, sugars, such as saccharides, including monosaccharides and polysaccharides, and carbohydrates, vitamins, steroids, steroid analogs,. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . used to target active plaque with evolving clots. Preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to

targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD [0305] Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD . . . to direct the present stabilizing materials, and particularly vesicle compositions, to the GIIbIIIa receptor. Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing, as well as treating such. . .

DETD [0307] Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1-(X.sup.1).sub.n-Arg-Tyr-Asp-(Y), --(X.sup.2).sub.m-R.sup.2, wherein. . .

DETD [0314] Other ligands usefull for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-amninobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD [0315] Generally, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0 368 486 A2, 0 382 451. .

DETD [0519] **GPIIbIIIa** binding peptide (Integrated Biomolecule Corporation, Tucson, Ariz.) was covalently bonded to DPPE-PEG 3400 to produce DPPE-PEG-Lys-Gln-Ala-Gly-Asp-Val, as follows. To a. . .

DETD . . . headspace replaced with perfluoromethylbutyl ether (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor (hereafter "thrombus-targeting contrast agent").

CLM What is claimed is:

. . . 18, wherein said targeting ligand targets cells or receptors selected from the group consisting of endothelial cells and the glycoprotein **GPIIbIIIa** receptor.

=> d l12 ibib ab kwic 11-15

L12 ANSWER 11 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2001:144937 USPATFULL
TITLE: Solid matrix therapeutic compositions
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
PATENT ASSIGNEE(S): ImaRx Therapeutics, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001018072	A1	20010830
APPLICATION INFO.:	US 2001-828762	A1	20010409 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-75477, filed on 11 May 1998, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-46379P	19970513 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Mackiewicz & Norris LLP, One Liberty Place - 46th Floor, Philadelphia, PA, 19103
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 4899
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a solid porous matrix comprising a surfactant in combination with a bioactive agent. The solid porous matrix may be prepared by combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and processing the emulsion by controlled drying, or controlled agitation and controlled drying to form the solid porous matrix.

DETD . . . tetrahydrofolate; peptides, such as angiostatin, manganese super oxide dismutase, tissue plasminogen activator, glutathione, insulin, dopamine, peptides with affinity for the **GPIIbIIIa** receptor (usually found on activated receptor platelets) such as RGD, AGD, RGE, KGD, KGE, and KQAGDV, opiate peptides (such as. . .

DETD [0138] DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 12 OF 18 USPATFULL on STN
ACCESSION NUMBER: 2001:71071 USPATFULL
TITLE: Methods for ultrasound imaging involving the use of a contrast agent and multiple images and processing of same
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
Fritz, Thomas A., Tucson, AZ, United States
Gertz, Edward W., Paradise Valley, AZ, United States
PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp., Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6231834	B1	20010515
APPLICATION INFO.:	US 1997-982829		19971202 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-932273, filed on 17 Sep 1997 Continuation-in-part of Ser. No. US 1996-666129, filed on 19 Jun 1996, now patented, Pat. No. US 6033645 Continuation-in-part of Ser. No. US 1996-660032, filed on 6 Jun 1996, now abandoned Continuation-in-part of Ser. No. US 1996-640464, filed on 1 May 1996, now abandoned Continuation-in-part of

Ser. No. US 1995-497684, filed on 7 Jun 1995, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hollinden, Gary E.
LEGAL REPRESENTATIVE: Woodcock Washburn Kurtz Mackiewicz & Norris LLP
NUMBER OF CLAIMS: 115
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 7574

AB Improved methods for providing an image of an internal region of a patient. Embodiments of the invention involve the administration to the patient of a contrast agent which comprises, in an aqueous carrier, a lipid, protein, polymer or surfactant, and a gas. The patient is scanned using ultrasound imaging to obtain a visible image of the region. In embodiments of the invention, the scanning step may comprise applying a first quantity of ultrasound energy to the patient to provide a first image, followed by the application substantially immediately thereafter of a second quantity of ultrasound energy to provide a second image. The first and second images are then processed. The methods are particularly useful for obtaining on-line images of the cardiovascular region which may be employed, for example, to diagnose the presence of diseased tissue in the cardiovascular region of a patient.

DETD . . . peptide hormones, neurotransmitters, antigens, complement fragments, and immunoglobulins and cytoplasmic receptors for steroid hormones. An exemplary receptor is the glycoprotein **GPIIbIIIa** which is a platelet integrin and which is frequently associated with coagula.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors. In particularly preferred embodiments, the targeting ligands may be especially suited for targeting cells or receptors associated with coagula,. . . from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material, including, for example, antibodies, **glycoproteins** and lectins, with proteins and peptides being preferred and peptides being more preferred. An example of a protein which may. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . known in the art. Targeting ligands derived or modified from human leukocyte origin, such as CD11a/CD18, and leukocyte cell surface **glycoprotein** (LFA-1), may also be used as these are known to bind to the endothelial cell receptor ICAM-1. The cytokine inducible. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. Conveniently, by attaching anti-myosin (particularly cardiomyosin) antibody. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor.

Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD . . . wide variety of targeting ligands may be employed to direct the present lipid compositions, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor may be highly useful for targeting coagulum, including vascular thromboses and/or emboli, and are useful for diagnosing, as well. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1 --(X.sup.1).sub.n --Arg-Tyr-Asp-(Y).sub.o. . .

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid), methanesulfonate salt. Peptides that can also be. . .

DETD Generally speaking, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in Sato et al., U.S. Pat. No. 5,498,601 and the following published European Patent Applications: 0. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, Q targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells and the glycoprotein **GPIIbIIIa** receptor. In addition, in embodiments where Q is a targeting ligand, Q is preferably selected from the group consisting of. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. Also in preferred embodiments, T is a targeting ligand selected from the group consisting of proteins, peptides, saccharides, steroids,. . .

DETD . . . of the vesicle. This may promote binding of the targeting ligands to targeting sites, for example, receptors, such as the **GPIIbIIIa** receptor, and tissues, including myocardial, endothelial and epithelial cells, since the targeting ligand has a greater likelihood of exposure to. . .

DETD **GPIIbIIIa** binding peptide (Integrated Biomolecule Corporation, Tucson, Ariz.) was covalently bonded to DPPE-PEG 3400 utilizing the procedure described above in Example. . . headspace replaced with perfluorobutane gas (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor.

DETD . . . be seen from the above table, binding was observed only with the vesicle composition prepared in Example 7 which contains **GPIIbIIIa** targeting peptide.

DETD . . . example is directed to the preparation of vesicles based on

human serum albumin that bear targeting ligands directed to the **GPIIbIIIa** receptor.

DETD . . . suspension will be added 1% glutaraldehyde and 1% by weight of the peptide Lys-Gln-Ala-Gly-Asp-Val resulting in crosslinked perfluoropropane vesicles bearing **GPIIbIIIa** binding peptide.

DETD . . . example is directed to the preparation of vesicles stabilized by polymerizable acryloyl/styryl lipid analogs binding targeting ligands directed to the **GPIIbIIIa** receptor.

DETD To a solution in normal saline of DPPE-PEG 5000 (1.8 mg/mL) and 10% by weight DPPE-PEG-5000 labelled with **GPIIbIIIa** binding peptide (Lys-Gln-Ala-Gly-Asp-Val), which will be prepared using the procedure described above in Example 5, will be added compound (3). . . . room temperature for about 1 minute. The vesicle composition will be irradiated (254 nm) to provide polymerized gas-filled vesicles bearing **GPIIbIIIa** binding peptide. The mean diameter of the vesicles will be about 3 .mu.m.

DETD This example is directed to the preparation of synthetic polybis(carboxylatophenoxy)phosphazene) (PCPP) gas-filled vesicles targeted to the **GPIIbIIIa** receptor.

DETD . . . be crosslinked by the divalent calcium ions to produce a relatively homogeneous population of spherical gel vesicles, targeted to the **GPIIbIIIa** and filled with perfluoropropane. The presence of entrapped perfluoropropane will be demonstrated by observation of the vesicles using an inverted. . .

DETD This example is directed to the preparation of a vesicles targeted to the **GPIIbIIIa** receptor formulated form a fluorinated lipid.

DETD . . . will be suspended in phosphate-buffered saline at a pH of 7. The peptide Arg-Gly-Asp-Ser (RGDS), which is targeted to the **GPIIbIIIa** receptor, will be added to the suspension. After stirring overnight, the reaction mixture will be concentrated with an Amicon filter. . . an ESPE Capmix (ESPE, Seefeld, Germany) at 4300 rpm for 1 minute to yield the fluorinated vesicle targeted to the **GPIIbIIIa** receptor.

DETD . . . pad. After the unbound clot was washed from the strip, 1 mL each of a targeted vesicle composition which targets **GPIIbIIIa** and the vesicle composition from Example 6 (non-targeted) was injected into the PBS stream at a flow rate of approximately. . . strip, while the non-targeted vesicles were washed away. Ultrasound imaging revealed increased echogenicity in the clot with vesicles targeted to **GPIIbIIIa**.

DETD . . . atrial thrombus by administering to the patients perfluorobutane gas filled lipid vesicles containing a peptide targeting ligand which targets the **GPIIbIIIa** receptor, and scanning the patient with echocardiography. The patients screened for episodes of AF by standard electrocardiography were found to. . .

DETD Perfluorobutane gas filled **GPIIbIIIa** targeted lipid vesicles were infused to provide a total dose of 0.03 mL/kg body weight. Using aseptic techniques, the proscribed. . .

L12 ANSWER 13 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2000:145865 USPATFULL

TITLE: Targeted contrast agents for diagnostic and therapeutic use

INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
Fritz, Thomas A., Tucson, AZ, United States
Gertz, Edward W., Paradise Valley, AZ, United States

PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp., Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6139819		20001031	
APPLICATION INFO.:	US 1997-932273		19970917	(8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-660032, filed			

on 6 Jun 1996, now abandoned which is a continuation-in-part of Ser. No. US 1996-640464, filed on 1 May 1996, now abandoned which is a continuation-in-part of Ser. No. US 1995-497684, filed on 7 Jun 1995, now abandoned And a continuation-in-part of Ser. No. US 1996-666129, filed on 19 Jun 1996, now patented, Pat. No. US 6033645

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Hartley, Michael G.
LEGAL REPRESENTATIVE: Woodcock Washburn Kurtz Mackiewicz & Norris LLP
NUMBER OF CLAIMS: 174
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 7523
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel contrast agents which may be used for diagnostic and therapeutic use. The compositions may comprise a lipid, a protein, polymer and/or surfactant, and a gas, in combination with a targeting ligand. In preferred embodiments, the targeting ligand targets coagula, including emboli and/or thrombi, particularly in patients suffering from an arrhythmic disorder. The contrast media can be used in conjunction with diagnostic imaging, such as ultrasound, as well as therapeutic applications, such as therapeutic ultrasound.

DETD . . . peptide hormones, neurotransmitters, antigens, complement fragments, and immunoglobulins and cytoplasmic receptors for steroid hormones. An exemplary receptor is the glycoprotein **GPIIbIIIa** which is a platelet integrin and which is frequently associated with coagula.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors. In particularly preferred embodiments, the targeting ligands may be especially suited for targeting cells or receptors associated with coagula,. . . from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material, including, for example, antibodies, **glycoproteins** and lectins, with proteins and peptides being preferred and peptides being more preferred. An example of a protein which may. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyaluronic. . .

DETD . . . known in the art. Targeting ligands derived or modified from human leukocyte origin, such as CD11a/CD18, and leukocyte cell surface **glycoprotein** (LFA-1), may also be used as these are known to bind to the endothelial cell receptor ICAM-1. The cytokine inducible. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. Conveniently, by attaching anti-myosin (particularly cardiomyosin) antibody. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD . . . wide variety of targeting ligands may be employed to direct the present lipid compositions, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor may be highly useful for targeting coagulum, including vascular thromboses and/or emboli, and are useful for diagnosing, as well. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets. Exemplary of such peptides include, for example, peptides of the general formula R.sup.1 --(X.sup.1).sub.n -Arg-Tyr-Asp-(Y).sub.o. . .

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD Generally speaking, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are disclosed, for example, in Sato et al., U.S. Pat. No. 5,498,601 and the following published European Patent Applications: 0. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. In certain preferred embodiments, Q targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells and the glycoprotein **GPIIbIIIa** receptor. In addition, in embodiments where Q is a targeting ligand, Q is preferably selected from the group consisting of. . .

DETD . . . cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein **GPIIbIIIa** receptor. Also in preferred embodiments, T is a targeting ligand selected from the group consisting of proteins, peptides, saccharides, steroids,. . .

DETD . . . of the vesicle. This may promote binding of the targeting ligands to targeting sites, for example, receptors, such as the **GPIIbIIIa** receptor, and tissues, including myocardial, endothelial and epithelial cells, since the targeting ligand has a greater likelihood of exposure to. . .

DETD **GPIIbIIIa** binding peptide (Integrated Biomolecule Corporation, Tucson, Ariz.) was covalently bonded to DPPE-PEG 3400 utilizing the procedure described above in Example. . . headspace replaced with perfluorobutane gas (Flura, Newport, Tenn.). The vials were agitated to provide a vesicle composition targeted to the **GPIIbIIIa** receptor.

DETD . . . be seen from the above table, binding was observed only with the vesicle composition prepared in Example 7 which contains

GPIIbIIIa targeting peptide.

DETD . . . example is directed to the preparation of vesicles based on human serum albumin that bear targeting ligands directed to the **GPIIbIIIa** receptor.

DETD . . . suspension will be added 1% glutaraldehyde and 1% by weight of the peptide Lys-Gln-Ala-Gly-Asp-Val resulting in crosslinked perfluoropropane vesicles bearing **GPIIbIIIa** binding peptide.

DETD . . . example is directed to the preparation of vesicles stabilized by polymerizable acryloyl/styryl lipid analogs binding targeting ligands directed to the **GPIIbIIIa** receptor.

DETD To a solution in normal saline of DPPE-PEG 5000 (1.8 mg/mL) and 10% by weight DPPE-PEG-5000 labelled with **GPIIbIIIa** binding peptide (Lys-Gln-Ala-Gly-Asp-Val), which will be prepared using the procedure described above in Example 5, will be added compound (3). . . . room temperature for about 1 minute. The vesicle composition will be irradiated (254 nm) to provide polymerized gas-filled vesicles bearing **GPIIbIIIa** binding peptide. The mean diameter of the vesicles will be about 3 .mu.m.

DETD This example is directed to the preparation of synthetic polybis(carboxylatophenoxy)phosphazene) (PCPP) gas-filled vesicles targeted to the **GPIIbIIIa** receptor.

DETD . . . be crosslinked by the divalent calcium ions to produce a relatively homogeneous population of spherical gel vesicles, targeted to the **GPIIbIIIa** and filled with perfluoropropane. The presence of entrapped perfluoropropane will be demonstrated by observation of the vesicles using an inverted. . .

DETD This example is directed to the preparation of a vesicles targeted to the **GPIIbIIIa** receptor formulated form a fluorinated lipid.

DETD . . . will be suspended in phosphate-buffered saline at a pH of 7. The peptide Arg-Gly-Asp-Ser (RGDS), which is targeted to the **GPIIbIIIa** receptor, will be added to the suspension. After stirring overnight, the reaction mixture will be concentrated with an Amicon filter. . . an ESPE Capmix (ESPE, Seefeld, Germany) at 4300 rpm for 1 minute to yield the fluorinated vesicle targeted to the **GPIIbIIIa** receptor.

DETD . . . pad. After the unbound clot was washed from the strip, 1 mL each of a targeted vesicle composition which targets **GPIIbIIIa** and the vesicle composition from Example 6 (non-targeted) was injected into the PBS stream at a flow rate of approximately. . . strip, while the non-targeted vesicles were washed away. Ultrasound imaging revealed increased echogenicity in the clot with vesicles targeted to **GPIIbIIIa**.

DETD . . . atrial thrombus by administering to the patients perfluorobutane gas filled lipid vesicles containing a peptide targeting ligand which targets the **GPIIbIIIa** receptor, and scanning the patient with echocardiography. The patients screened for episodes of AF by standard electrocardiography were found to. . .

DETD Perfluorobutane gas filled **GPIIbIIIa** targeted lipid vesicles were infused to provide a total dose of 0.03 mL/kg body weight. Using aseptic techniques, the proscribed. . .

L12 ANSWER 14 OF 18 USPATFULL on STN

ACCESSION NUMBER: 2000:127960 USPATFULL

TITLE: Optoacoustic contrast agents and methods for their use

INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
Wu, Yunqiu, Tucson, AZ, United States

PATENT ASSIGNEE(S): Imarx Pharmaceutical Corp., Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6123923		20000926	
APPLICATION INFO.:	US 1997-993165		19971218	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-46379P	19970513 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Sharareh, Shahnam
LEGAL REPRESENTATIVE: Woodcock Washburn Kurtz Mackiewcz & Norris LLP
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 6923
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention generally relates to optoacoustic contrast agents and methods of diagnostic and therapeutic imaging using optoacoustic contrast agents.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors.

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . used to target active plaque with evolving clots. Preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDI, and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; pharmaceuticals, such as drugs, including the alpha. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeted ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which may be. .

DETD A wide variety of targeting ligands may be employed to direct the present compositions, and particularly vesicle compositions, to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing, as well as treating such. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and which may bind to the **GPIIbIIIa** binding region on activated platelets.

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD Generally, it is preferred to employ as targeting ligands for the **GPIIbIIIa** receptor a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD . . . peptides which would be suitable for use as a targeting ligand in connection with the present invention, especially for targeting **GPIIbIIIa**, are described, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0 368 486 A2, 0 382 451. .

DETD . . . activator (t-PA), glutathione, insulin, dopamine, peptide ligands containing RGD, AGD, RGE, KGD, KGE or KQAGDV (Peptides with affinity for the **GPIIBIIIa** receptor), opiate peptides, enkephalins, endorphins and their analogs, human chorionic gonadotropin (HCG), corticotropin release factor (CRF), cholecystokinins and their analogs,. . .

DETD . . . of Ras. DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interlcukin-2 may be provided to treat advanced cancers;. . .

L12 ANSWER 15 OF 18 USPATFULL on STN

ACCESSION NUMBER:	2000:124531 USPATFULL
TITLE:	Charged lipids and uses for the same
INVENTOR(S):	Unger, Evan C., Tucson, AZ, United States
PATENT ASSIGNEE(S):	ImaRx Pharmaceutical Corp., Tucson, AZ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6120751		20000919
APPLICATION INFO.:	US 1997-925353		19970908 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-823791, filed on 21 Mar 1997 And a continuation-in-part of Ser. No. US 1997-851780, filed on 6 May 1997 And a continuation-in-part of Ser. No. US 1997-877826, filed on 18 Jun 1997 And a continuation-in-part of Ser. No. US 1997-887215, filed on 2 Jul 1997

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Dees, Jose' G.
ASSISTANT EXAMINER:	Hartley, Michael G.
LEGAL REPRESENTATIVE:	Woodcock Washburn Kurtz Mackiewicz & Norris LLP
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT:	6059

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to charged lipids, compositions comprising charged lipids, and the use of these compositions in drug delivery, targeted drug delivery, therapeutic imaging and diagnostic imaging, as well as their use as contrast agents.

DETD . . . membranous tissues, including endothelial and epithelial cells. In the case of receptors, the targeting ligands are desirably capable of targeting **GPIIbIIIa** receptors or lymphocyte receptors, such as T-cells, B-cells or interleukin-2 receptors. Preferred targeting ligands for use in targeting tissues and/or. . . tissues and receptors exemplified above, are selected from the group consisting of proteins, including antibodies, antibody fragments, hormones, hormone analogues, **glycoproteins** and lectins, peptides, polypeptides, amino acids, sugars, such as saccharides, including monosaccharides and polysaccharides, and carbohydrates, vitamins, steroids, steroid

analogs,. . .

DETD . . . non-peptide angiogenic factors, such as 1-butyryl glycerol; the prostaglandins, including, for example, prostaglandin E.sub.1 (PGE.sub.1) and prostaglandin E.sub.2 (PGE.sub.2); nicotinamide; **adenosine**; dipyridamole; dobutamine; hyaluronic acid degradation products, such as, for example, degradation products resulting from hydrolysis of .beta. linkages, including hyalobiuronic. . .

DETD . . . to target active plaque with evolving clots. Most preferred targeting ligands are those which will target a plasma membrane associated **GPIIbIIIa** in activated platelets in addition to targeting P-selectin, and an antibody or associated antibody fragment directed to **GPIIbIIIa**. The present invention is also useful for detecting regions of acute myocardial infarction. By attaching anti-myosin (particularly cardiomyosin) antibody or. . .

DETD . . . density lipoproteins (LDL), including .alpha.-LDL, vLDL and methyl LDL; ryanodine; endothelin; complement receptor type 1; IgG Fc; beta 1-adrenergic; dihydropyridine; **adenosine**; mineralocorticoid; nicotinic acetylcholine and muscarinic acetylcholine; antibodies to the human alpha 1A-adrenergic receptor; bioactive agents, such as drugs, including the. . .

DETD Two of the major antigens of heart sarcolemmal are calcium binding **glycoproteins** which copurify with the dihydropyridine receptor. Antisera may be raised, including polyclonal or monoclonal antibodies, against purified sarcolemma. These antibodies may also be employed as targeting ligands. Purified fractions of the calcium binding **glycoproteins** may be isolated from the plasma membranes of the sarcolemma and then used to generate antibodies. ANP, which, as noted. . .

DETD A wide variety of targeting ligands may be employed to direct the present compositions to the **GPIIbIIIa** receptor. Compositions which are directed to the **GPIIbIIIa** receptor are highly useful for targeting vascular thromboses or clots, and are useful for diagnosing and treating such clots. Included. . .

DETD Additional peptides which may be useful as targeting ligands for targeting the **GPIIbIIIa** receptor include, for example, peptides comprising the tripeptide sequence of arginine-tyrosine-aspartic acid (Arg-Tyr-Asp; also abbreviated RGD), linked from amino-to-carboxy-terminus and. . .

DETD Other ligands useful for targeting the **GPIIbIIIa** receptor include synthetic compounds, such as Ac-(D)Phe-Pro-boroArg and the cyclic peptidomimetic cyclo(D-2-aminobutyrate-N-Methyl-L-Arginyl-Glycyl-L-Aspartyl-3-amino-methyl-benzoic acid) methanesulfonate salt. Peptides that can also be. . .

DETD Generally, it is preferred to employ, as targeting ligands for the **GPIIbIIIa** receptor, a peptide having from about 3 to about 20 amino acids, with peptides having from about 4 to about 15 amino acids being more preferred. Even more preferably, targeting ligands for the **GPIIbIIIa** receptor may comprise peptides having from about 4 to about 8 amino acids, with peptides having from about 4 to. . .

DETD Various peptides which would be suitable for use as a targeting ligand in the present invention, especially for targeting **GPIIbIIIa**, are described, for example, in U.S. Pat. No. 5,498,601 and European Patent Applications: 0 368 486 A2, 0 382 451. . .

DETD DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, **adenosine** deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers;. . .